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MEDICAL ECONOMICS
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NAPROSYN (naproxen) Suspension for oral administration contains 125 mg/5 mL of naproxen in a vehicle containing sucrose, magnesium aluminum silicate, sorbitol solution and sodium chloride (30 mg/5 mL, 1.5 mEq), methylparaben, fumaric acid, FD&C Yellow No. 6, imitation pineapple flavor, imitation orange flavor and purified water. The pH of the suspension ranges from 2.2 to 3.7.

CLINICAL PHARMACOLOGY

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

Pharmacokinetics: Naproxen itself is rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. The different dosage forms of NAPROSYN are bioequivalent in terms of extent of absorption (AUC) and peak concentration (C_{max}), however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical form of naproxen used and its formulation. Even with the observed differences in pattern of absorption, the elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negligible role in the attainment of steady-state plasma levels.

Absorption:

Immediate Release: After administration of NAPROSYN tablets, peak plasma levels are attained in 2 to 4 hours. After oral administration of ANAPROX, peak plasma levels are attained in 1 to 2 hours. The difference in rates between the two products is due to the increased aqueous solubility of the sodium salt of naproxen used in ANAPROX. Peak plasma levels of naproxen given as NAPROSYN Suspension are attained in 1 to 4 hours.

Delayed Release: EC-NAPROSYN is designed with a pH-sensitive coating to provide a barrier to disintegration in the acidic environment of the stomach and to lose integrity in the more neutral environment of the small intestine. The enteric polymer coating selected for EC-NAPROSYN dissolves above pH 6. When EC-NAPROSYN was given to fasted subjects, peak plasma levels were attained about 4 to 6 hours following the first dose (range: 2 to 12 hours). An in vivo study in man using radiolabeled EC-NAPROSYN tablets demonstrated that EC-NAPROSYN dissolves primarily in the small intestine rather than the stomach, so the absorption of the drug is delayed until the stomach is emptied. When EC-NAPROSYN and NAPROSYN were given to fasted subjects (n=24) in a crossover study following 1 week of dosing, differences in time to peak plasma levels (T_{max}) were observed, but there were no differences in total absorption as measured by C_{max} and AUC:

[See table below]

Antacid Effects: When EC-NAPROSYN was given as a single dose with antacid (54 mEq buffering capacity), the peak plasma levels of naproxen were unchanged, but the time to peak was reduced (mean T_{max}, fasted 5.6 hours, mean T_{max} with antacid 5 hours), although not significantly.

Food Effects: When EC-NAPROSYN was given as a single dose with food, peak plasma levels in most subjects were achieved in about 12 hours (range: 4 to 24 hours). Residence time in the small intestine until disintegration was independent of food intake. The presence of food prolonged the time the tablets remained in the stomach, time to first detectable serum naproxen levels, and time to maximal naproxen levels (T_{max}), but did not affect peak naproxen levels (C_{max}).

Distribution:

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance cause by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen). However, the concentration of unbound naproxen continues to increase proportionally to dose.

Metabolism:

Naproxen is extensively metabolized to 6-O-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes.

Elimination:

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-O-desmethyl naproxen (less than 1%) or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans, both after NAPROSYN medication and conjugates, are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure metabolites may accumulate.

Special Populations:

Pediatric Patients: In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see DOSAGE AND ADMINISTRATION) were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen suspension or tablets in pediatric patients. EC-NAPROXYN has not been studied in subjects under the age of 18.

Renal Insufficiency: Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency.

CLINICAL STUDIES

General Information: Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute gout. Improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time. Generally, response to naproxen has not been found to be dependent on age, sex, severity or duration of rheumatoid arthritis.

In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In a clinical trial comparing standard formulations of naproxen 375 mg bid (750 mg a day) vs 750 mg bid (1500 mg/day), 9 patients in the 750 mg group terminated prematurely because of adverse events. Nineteen patients in the 1500 mg group terminated prematurely because of adverse events. Most of these adverse events were gastrointestinal events.

In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, naproxen has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less in naproxen-treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

In patients with acute gout, a favorable response to naproxen was shown by significant clearing of inflammatory changes (eg, decrease in swelling, heat) within 24 to 48 hours, as well as by relief of pain and tenderness.

Naproxen has been studied in patients with mild to moderate pain secondary to postoperative, orthopedic, postpartum episiotomy and uterine contraction pain and dysmenorrhea. Onset of pain relief can begin within 1 hour in patients taking naproxen and within 30 minutes in patients taking naproxen sodium. Analgesic effect was shown by such measures as reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time to remedication. The analgesic effect has been found to last for up to 12 hours.

Naproxen may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids, it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether naproxen has a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs, the combination may result in higher frequency of adverse events than demonstrated for either product alone.

	EC-NAPROSYN* 500 mg bid	NAPROSYN* 500 mg bid
C_{max} (µg/mL)	94.9 (18%)	97.4 (13%)
T_{max} (hours)	4 (39%)	1.9 (61%)
$AUC_{0-12\,hr}$ (µg•hr/mL)	845 (20%)	767 (15%)

* Mean value (coefficient of variation)

1000 mg of NAPROSYN (naproxen) or 1100 ANAPROX (naproxen sodium) has been demonstr... cause statistically significantly less gastric bleedi... erosion than 3250 mg of aspirin.

Three 6-week, double-blind, multicenter studies wi... NAPROSYN (naproxen) (375 or 500 mg bid, n=3... NAPROSYN (375 or 500 mg bid, n=279) were co... comparing EC-NAPROSYN with NAPROSYN, inc... 355 rheumatoid arthritis and osteoarthritis patient... had a recent history of NSAID-related GI symptoms... studies indicated that EC-NAPROSYN and NAPR... showed no significant differences in efficacy or sa... had similar prevalence of minor GI complaints. Indi... patients, however, may find one formulation prefer... the other.

Five hundred and fifty-three patients received... NAPROSYN during long-term open label trials ... length of treatment was 159 days). The rates for cli... diagnosed peptic ulcers and GI bleeds were similar to... has been historically reported for long-term NSAID ...

INDIVIDUALIZATION OF DOSAGE

Although NAPROSYN, NAPROSYN Suspension, NAPROSYN, ANAPROX and ANAPROX DS all circu... the plasma as naproxen, they have pharmacokinetic... ences that may affect onset of action. Onset of pain... can begin within 30 minutes in patients taking na... sodium and within 1 hour in patients taking napro... cause EC-NAPROSYN dissolves in the small in... rather than in the stomach, the absorption of the ... delayed compared to the other naproxen formulati... CLINICAL PHARMACOLOGY).

The recommended strategy for initiating th... choose a formulation and a starting dose likely to ... tive for the patient and then adjust the dosage based ... servation of benefit and/or adverse events. A low... should be considered in patients with renal or hepa... pairment or in elderly patients (see PRECAUTIONS).

Analgesia/Dysmenorrhea/Bursitis and Tendonitis: ... cause the sodium salt of naproxen is more rapidly ab... ANAPROX/ANAPROX DS is recommended for the m... ment of acute painful conditions when prompt onset o... relief is desired. The recommended starting dose is ... followed by 550 mg every 12 hours or 275 mg every ... hours, as required. The initial total daily dose shou... exceed 1375 mg of naproxen sodium. Thereafter, th... daily dose should not exceed 1100 mg of naproxen ... NAPROSYN may also be used for treatment of acu... and dysmenorrhea. EC-NAPROSYN is not recomm... for initial treatment of acute pain because absorp... naproxen is delayed compared to other naproxen-co... products (see CLINICAL PHARMACOLOGY and IN... TIONS AND USAGE).

Acute Gout: The recommended starting dose is 75... NAPROSYN followed by 250 mg every 8 hours until ... tack has subsided. ANAPROX may also be used at ... ing dose of 825 mg followed by 275 mg every 8 h... needed. EC-NAPROSYN is not recommended because ... delay in absorption (see CLINICAL PHARMACOLOG...

Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis: The recommended dose of naproxen is NAPRO... NAPROSYN Suspension 250 mg, 375 mg or 500 mg ... twice daily (morning and evening) or EC-NAPROSY... mg or 500 mg taken twice daily. Naproxen sodium ... be used (see DOSAGE AND ADMINISTRATION).

During long-term administration the dose of napro... be adjusted up or down depending on the clinical ... of the patient. A lower daily dose may suffice for l... administration. In patients who tolerate lower do... the dose may be increased to 1500 mg per day ... higher level of anti-inflammatory/analgesic activity ... quired. When treating patients with naproxen 1500 ... (as NAPROSYN or 1650 mg of ANAPROX), the p... should observe sufficient increased clinical benefit to... the potential increased risk. The morning and ... doses do not have to be equal in size and administ... the drug more frequently than twice daily does not ... ally make a difference in response (see CLINICAL ... MACOLOGY).

Juvenile Arthritis: The use of NAPROSYN Suspen... lows for more flexible dose titration. In pediatric p... doses of 5 mg/kg/day produced plasma levels of n... similar to those seen in adults taking 500 mg of n... (see CLINICAL PHARMACOLOGY).

The recommended total daily dose is approxim... mg/kg given in two divided doses (ie, 5 mg/kg give... day) (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Naproxen as NAPROSYN, EC-NAPROSYN, AN... ANAPROX DS or NAPROSYN Suspension are ind... the treatment of rheumatoid arthritis, osteoarthri... losing spondylitis and juvenile arthritis.

Naproxen as NAPROSYN Suspension is recomm... juvenile rheumatoid arthritis in order to obtain ... mum dosage flexibility based on the patient's we...

Naproxen as NAPROSYN, ANAPROX, ANAPRO... NAPROSYN Suspension are also indicated for ... ment of tendonitis, bursitis, acute gout, and for the ... ment of pain and primary dysmenorrhea. EC-NA... is not recommended for initial treatment of acu... cause the absorption of naproxen is delayed comp...